

Is survival really better after repeated lung metastasectomy?

Francesca Fiorentino

Department of Surgery and Cancer, Imperial College London, London UK

Tom Treasure*

0000-0001-9358-7610

Clinical Operational Research Unit, University College London, London, UK

*corresponding author tom.treasure@gmail.com

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Abstract

159 words

Several groups have observed that average survival time after a second lung metastasectomy is longer than after a first metastasectomy. The randomised controlled trial Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) found no survival benefit from lung metastasectomy. In fact, median survival was longer, and four-year overall survival was higher, in the control group than in those randomly assigned to metastasectomy, although not significantly so. The illusion of benefit is because survival without metastasectomy has been assumed to be near zero, as stated in Society of Thoracic Surgeons' Expert Consensus Document on Pulmonary Metastasectomy 2019. It has been repeatedly found that survival is influenced by the selection of patients who have characteristics associated with better prognosis. The passage of time while monitoring and assessing patients, and observing their rate of progression, provides for immortal time bias. Reselection of the most favourable patients for repeated metastasectomy is the likely reason for any differences in survival between first and repeated metastasectomy operations.

Is survival really better after repeated metastasectomy?

This is an intriguing question. The first operation failed in its ultimate objective, which was to remove all the residual colorectal cancer and thus cure the patient, and yet there is longer survival after repeated operations. How does it come about that having a second metastasectomy is associated with longer survival than after a first operation? The phenomenon has been observed in at least four of the observational studies in the list of references in the paper by Dr Forster and colleagues.(1) We addressed the matter in an Editorial in the Journal of Thoracic and Cardiovascular Surgery five years ago, using data from the work of the late Professor Mineo(2) and we have reconsidered the conundrum in the light of this new study.(1)

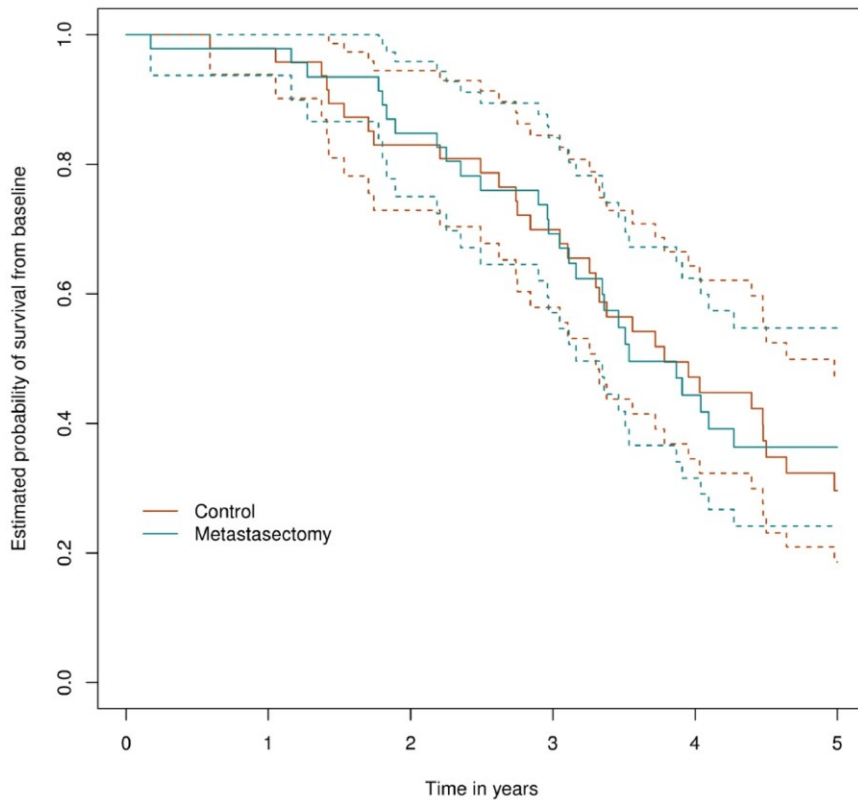
The first place to look for a possible explanation is in the Kaplan-Meier curves in Fig.1 because that is the most readily grasped presentation of the data and contains the time to death of all 246 patients. It should have numbers at risk because towards the right when there are large steps down, and long flat lines, it looks as though there are very few patients being represented, and we should be given that information. Confidence Intervals would be informative also. But the left-hand part of the two curves is interpretable.(3)

1. The early parts of the curves are markedly different. We know that in the short term, lung-metastasectomy is not life-saving surgery. The separation of the curves in the first year or so cannot be attributed to an effect of lung metastasectomy because patients with imminently lethal patterns of disease are selected out.
2. Among the patients who had just one metastasectomy operation, the proportion alive begins to fall, and does so quite steeply within about six months. We can be fairly confident that the lung metastasis was not the fatal component of the disease. The rapidity of progress in the liver, abdomen and pelvis is the usual reason in colorectal cancer which is the most frequent cancer in the series.
3. The curve for those selected to have a second metastasectomy operation has a plateau which lasts for about 18 months. This is the effect of immortal time bias. It is seen well in a big data analysis of liver resection.(3) The patients with aggressive disease have been excluded by the passage of time involved in first metastasectomy. When lung metastases appear again, there is a built-in period of monitoring. If liver or other metastases are progressing, particular if this is despite chemotherapy, these patients are unlikely to enter the second lung metastasectomy cohort. The length of time during which patients haven't died before operation (a death free interval or "immortal" time) is a good predictor of how long they will live afterwards.
4. The effect goes on with selection for subsequent repeated metastasectomies. Remember that there is bound to be a statistical association between survival and the number of repeat metastasectomy operations, but it is reverse causation. Longer survival leads to more opportunities for treatment, and each treatment takes time to plan and to recover from.

Finally, beware of resorting to sophisticated analysis before considering the suitability of the data for this approach. Hazard ratios serve well in comparing the arms of a randomised trial

but there is a danger in comparing survival between fundamentally dissimilar groups with this very powerful tool.(3) The shapes of the KM curves show the patient groups to be dissimilar in their behaviour. In the PulMiCC trial, published this year with all 93 randomised patients, the median survival for the metastasectomy arm was 3.5 years (95%CI:3.1-6) and was longer, although not significantly so, in the control arm at 3.8 years (95%CI:3.1-4.6).(4) In considering these results it is important to remember that the power calculation was to plan a trial of for non-inferiority. Cox warned that the power calculation is “quite irrelevant in the actual analysis of data”.

So we think that his phenomenon, of the second metastasectomy appearing to give greater benefit than the first, is due to selection upon selection.(2) Based on RCT evidence survival benefit after a first lung metastasectomy for colorectal cancer is questionable, and based on logical reasoning, survival benefit from a second metastasectomy is unlikely. The practice lung metastasectomy in colorectal cancer was based on the assumption that there is near zero survival by five years, now shown to untrue.(5)



47	46	39	32	20	13
46	45	39	31	17	13

Legend. The Kaplan Meier analysis of the Pulmonary Metastasectomy in Colorectal Cancer randomised controlled trial. He dashed lines are 95% Confidence Intervals.

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